IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, Charles Christopher Evans declare

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland, residing at 33 Farfield Road, Shipley, West Yorkshire, BD18 4QP.

2. That I am well acquainted with the English and Chinese languages.

3. That the attached is a true translation into the English language of the certified copy of Chinese Patent Application No. 02121479.4 filed on 25th June 2002.

4. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the patent application in the United States of America or any patent issuing thereon.

DECLARED THIS 27th DAY OF OCTOBER 2004

C C Evans *(SIGNATURE)*

Charles Christopher Evans *(printed name)*

CERTIFICATION

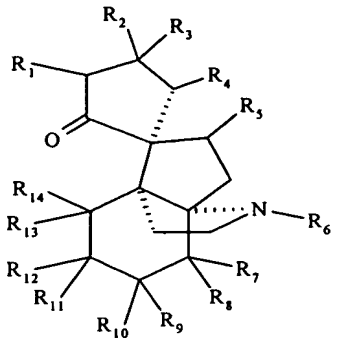
It is hereby certified that the attachment is a copy of the following Patent Application filed with this Office:

Date of filing:	25 June 2002
Application No.:	02 1 21479.4
Category of Application:	Invention
Title of invention:	Acutumine and acutumine compounds, synthesis and applications
Applicants:	SHANGHAI INSTITUTE OF MATERIA MEDICA, Chinese Academy of Sciences, LES LABORATOIRES SERVIER
Inventors or designers:	Qin Guowei, Tang Xican, P.Lestage, D-H.Caignard, P.Renard

Wang Jingchuan
Director,
State Intellectual Property Office,
People's Republic of China.
21 September 2004

CLAIMS

1. Compounds of formula (I) :



(I),

wherein

- R_1 and R_2 each represent a hydrogen atom or together constitute an extra bond,
- R_3 represents a hydrogen atom or an alkoxy group,
- R_4 represents a hydrogen atom or a hydroxy, alkoxy, alkylcarbonyloxy or arylcarbonyloxy group,
- R_5 represents a hydrogen or halogen atom,
- R_6 represents a hydrogen atom or an alkyl, alkylcarbonyl or aroyl group,
- R_7 represents an alkoxy group,
- R_8 and R_9 together constitute an extra bond,
  or R_8 and R_{13} together constitute a sulphide bridge, in which case R_9 and R_{10} together constitute an oxo group and R_{14} represents a chlorine atom,
- R_{10} represents an alkoxy group,
- R_{11} represents a hydroxy or alkoxy group,
- R_{12} represents a hydrogen atom,
  or R_{11} and R_{12} together constitute an oxo, oxime or O-alkyl-oxime group,
- R_{13} and R_{14} each represent a hydrogen atom or together constitute an oxo group,

with the proviso that the compound of formula (I) cannot represent :

- spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumine)
- spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]

- spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-acetylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-hydroxy-cyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol]
- spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-benzoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-acetyl-cyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumidine)
- spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

and wherein it should be understood that

- "alkyl" denotes an alkyl group containing 1 to 6 carbon atoms, which may be linear or branched,
- "alkoxy" denotes an alkoxy group containing 1 to 6 carbon atoms, which may be linear or branched,
- "aryloxy" denotes an aryloxy group wherein the aryl moiety represents phenyl or naphthyl,
- "aroyl" denotes an arylcarbonyl group wherein the aryl moiety represents phenyl or naphthyl,

their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases.

2. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein on the one hand R_1 and R_2, and on the other hand R_8 and R_9, together constitute an extra bond.

3. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein the groups R_3, R_7 and R_{10} each represent a methoxy group.

4. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein R_4 represents a hydroxy, acetyloxy or benzoyloxy group.

5. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein R_5 represents a chlorine atom.

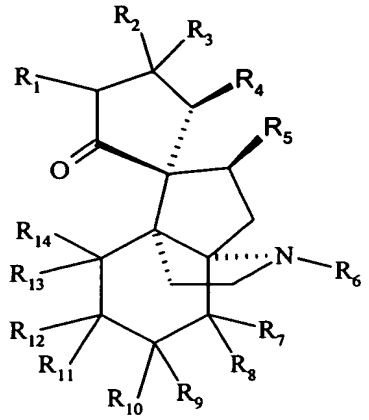
6. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein R_6 represents a methyl or ethyl group.

7. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein R_6 represents a hydrogen atom.

8. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein R_{11} and R_{12} together constitute an oxo group.

9. The compounds of formula (I), their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases as set down in Claim 1 wherein R_{13} and R_{14} each represent a hydrogen atom.

10. The compounds of formula (I) set down in Claim 1 that have the configuration shown by formula (I'):

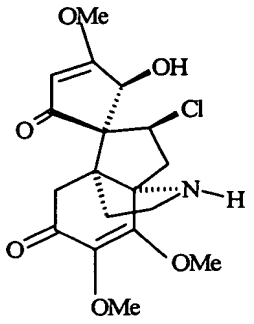


(I'),

their enantiomers and diastereoisomers, and their addition salts with pharmaceutically acceptable acids or bases.

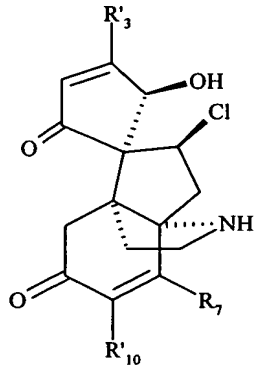
11. The compounds of formula (I) set down in Claim 1, their enantiomers and addition salts with pharmaceutically acceptable acids or bases, that comprise the compounds spiro[(4S,5S)-4-(ethoxycarbonyl)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-ethylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-(ethoxycarbonyl)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-propanoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one oxime], spiro[(4S,5S)-3,4-dimethoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-2,3,3a,7a-tetrahydro-4*H*,5*H*-indene-4,5-dione], spiro[(5S)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-hydroxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol], spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2,4-dichloro-3aS, 7aS-((2,3)-1-methylpyrrolidine)-7-methoxy-8-thiabicyclo[2.2.1]-1,2,3,3a,4,7a-hexahydro-5*H*,6*H*-indene-5,6-dione].

12. A process for preparation of the compounds of formula (I) set down in Claim 1 characterised in that the compound of formula (II) is used as starting material:



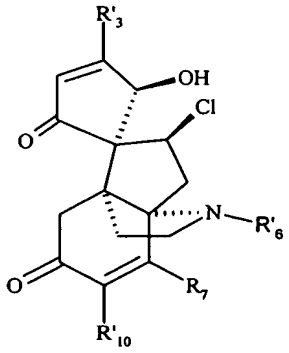
(II),

the compound of formula (II) is successively subjected to the action of a demethylating agent and an alkylating agent to obtain the compound of formula (I/a), a particular case of the compounds of formula (I) :



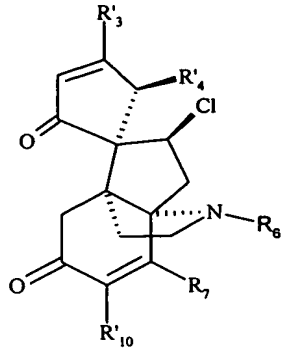
(I/a),

wherein R'_3 and R'_{10} each represent an alkoxy group and R_7 is as defined for formula (I),
which may be reacted with a compound of formula $R_{15}CHO$ (wherein R_{15} represents an alkyl group) in a reducing medium to obtain the compound of formula (I/b), a particular case of the compounds of formula (I) :



(I/b),

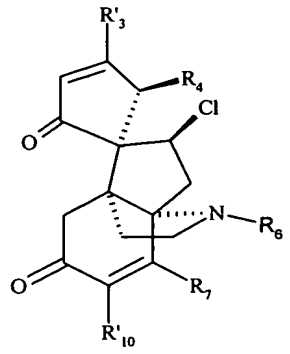
wherein R'_3, R_7 and R'_{10} are as hereinbefore defined and R'_6 represents an alkyl group; the compounds of formula (II), (I/a) or (I/b) may be reacted with a compound of formula $(R_{16}CO)_2O$ (wherein R_{16} represents an alkyl or aryl group) to obtain the compound of formula (I/c), a particular case of the compounds of formula (I) :



(I/c),

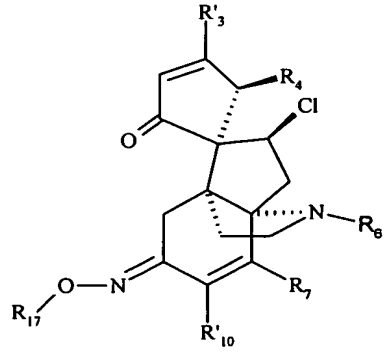
wherein R'_3, R_7 and R'_{10} are as hereinbefore defined, R_6 is as defined for formula (I) and R'_4 represents a hydroxy, alkylcarbonyloxy or arylcarbonyloxy group;

or compounds of formula (II), (I/a), (I/b) or (I/c) may be reacted with a compound of formula $E\text{-}R_{15}$ (wherein R_{15} represents an alkyl group and E represents a leaving group such as a halogen atom or a tosyl group) to obtain the compound of formula (I/d), a particular case of the compounds of formula (I) :



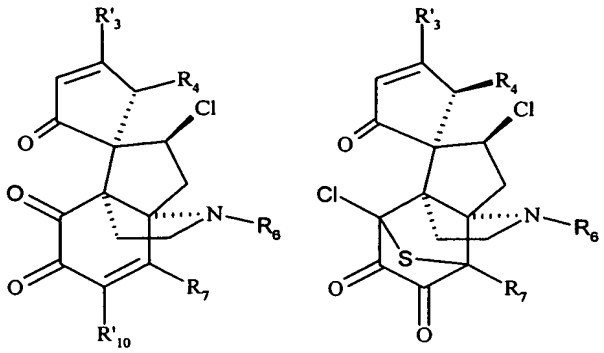
(I/d),

wherein R'_3, R_6, R_7 and R'_{10} are as defined hereinbefore and R_4 is as defined for formula (I);
the compound of formula (I/d) may be reacted with the compound of formula $R_{17}ONH_2$ (wherein R_{17} represents a hydrogen atom or an alkyl group) to obtain the compound of formula (I/e), a particular case of the compounds of formula (I) :



(I/e),

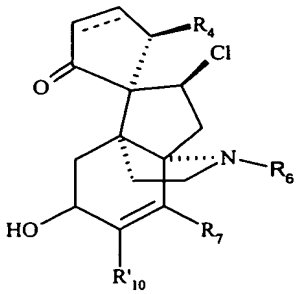
wherein R'_3, R_4, R_6, R_7, R'_{10} and R_{17} are as hereinbefore defined;
or the compound of formula (I/d) may be reacted with $SOCl_2$/DMF to obtain the compounds of formula (I/f), particular cases of the compounds of formula (I) :



(I/f),

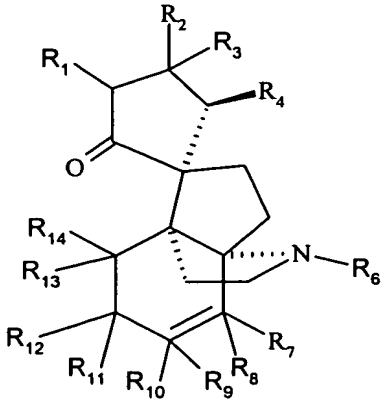
wherein R'_3, R_4, R_6, R_7 and R'_{10} are as defined hereinbefore;

or the compound of formula (I/d) may be reacted with a reducing agent such as $LiAlH_4$ to obtain the compound of formula (I/g), a particular case of the compounds of formula (I) :



(I/g),

wherein R_4, R_6, R_7 and R'_{10} are as hereinbefore defined and the symbol ----- indicates that the bond in question may be a single or a double bond;
or the compound of formula (I/d), (I/e), (I/f) or (I/g) may be reacted with n-Bu_3SnH in the presence of AIBN to obtain the compounds of formula (I/h), particular cases of the compounds of formula (I):



(I/h),

wherein R_4, R_6 and R_7 are as hereinbefore defined and R_1, R_2, R_3, R_5, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are as defined for formula (I), and
the compounds of formulae (Ia) to (Ih) constitute the totality of the compounds of the invention, which may be purified in accordance with conventional separation techniques and if necessary, converted into their addition salts with pharmaceutically acceptable acids or bases and where appropriate separated into their isomers in accordance with conventional separation techniques.

13. Pharmaceutical compositions comprising at least one of the compounds of formula (I) set down in any one of Claims 1 to 11 or an addition salt thereof with a pharmaceutically acceptable acid or base, together with one or more pharmaceutically acceptable excipients.

14. The pharmaceutical compositions set down Claim 13 for use in the preparation of drugs for the treatment of memory deficit associated with cerebral ageing and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

15. The use of acutumine and/or acutumine compounds in the preparation of pharmaceutical compositions, the said pharmaceutical compositions being used for the treatment of memory deficit associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

16. The use of acutumine in the preparation of pharmaceutical compositions as set down in Claim 15, the said pharmaceutical compositions being used for the treatment of memory deficit associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

17. The use of acutumine compounds in the preparation of pharmaceutical compositions as set down in Claim 15, the said pharmaceutical compositions being used for the treatment of memory deficit associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

18. The use of spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumine), spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-acetylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-(benzoyloxy)-

3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-hydroxycyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol], spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-benzoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-acetylcyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumidine), spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], or spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] in the preparation of pharmaceutical compositions as set down in Claim 15, the said pharmaceutical compositions being used for the treatment of memory deficit associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

19. Pharmaceutical compositions comprising acutumine or an acutumine compound together with one or more pharmaceutically acceptable excipients, the said pharmaceutical compositions being used for the treatment of memory deficit associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

SPECIFICATION

Acutumine and acutumine compounds, synthesis and applications

The Asiatic moonseed *Menispermum dauricum,* a ligneous climbing plant growing to more than ten metres, is widely distributed throughout Northern, North-Eastern and Eastern China (National Collective Data of Chinese Traditional and Herbal Medicines Editorial Board, "National Collective Data of Chinese Traditional and Herbal Medicines", People's Health Publishing House, First Edition (Chinese), 1975, p.105). The dried rhizome, designated *beidougen* (Rhizoma Menispermi), is a component of Chinese herbal medicines and now officially included as an analgesic and antipyretic in the Chinese Pharmacopoeia (Pharmacopoeia Committee of the People's Republic of China, 2000).

The active components of *Menispermum dauricum* are mainly alkaloids (1 to 2 % of the crude extract). Numerous alkaloids of various structure, such as bisbenzyl-isoquinoline, oxoisoaporphine, aporphine, proaporphine and morphinan, have been isolated and characterised.

A great number of the alkaloids have been purified and studied for their pharmacological properties. For example, dauricine, a major alkaloid constituent of the rhizome, has been found to possess cardiovascular system activity and anti-inflammatory properties. It has been used clinically for treating arrhythmia patients.

Dahurisoline, another alkaloid of bisbenzylisoquinoline structure, exhibits muscle-relaxant effects (Liu Chang-Xiao *et al.*, "Modern Research and Application of Chinese Medicinal Plants", Hong Kong Medical Publisher, First Edition (English), 2000, p.480).

Acutumine, a minor alkaloid constituent of the rhizome, was discovered in 1967 and has special characteristics owing to the presence of a chlorine atom (Tomita, M. *et al.*, *Chemical and Pharmaceutical Bulletin*, 1971, 19(4), p.770). We have now discovered that acutumine has mnemocognitive enhancement properties in experimental animal models.

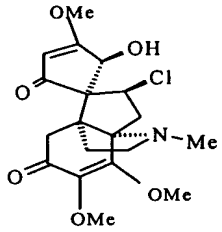
The ageing of the population due to increased life expectancy has brought about a major increase in cognitive disorders associated with normal cerebral ageing or the pathological cerebral ageing that occurs in the course of neurodegenerative diseases such as Alzheimer's disease.

The majority of substances currently used in treating senility-related cognitive disorders act by stimulating the central cholinergic system – either directly in the case of acetylcholinesterase inhibitors (tacrine, donepezil) and cholinergic agonists

(nefiracetam), or indirectly in the case of nootropic agents (piracetam, pramiracetam) and cerebral vasodilators (vinpocetine).

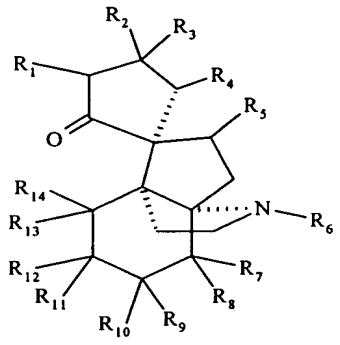
Particular importance therefore attaches to the synthesis of novel compounds capable of counteracting senility-related cognitive disorders and/or improving the cognitive process.

The present invention relates, on the one hand, to the use of acutumine



and/or acutumine compounds in mnemocognitive disorders and, on the other hand, to the synthesis of new compounds with especially valuable pharmacological properties in the same area.

The invention relates more specifically to compounds of formula (I) :



(I),

wherein

- R_1 and R_2 each represent a hydrogen atom or together constitute an extra bond,
- R_3 represents a hydrogen atom or an alkoxy group,
- R_4 represents a hydrogen atom or a hydroxy, alkoxy, alkylcarbonyloxy or arylcarbonyloxy group,
- R_5 represents a hydrogen or halogen atom,
- R_6 represents a hydrogen atom or an alkyl, alkylcarbonyl or aroyl group,
- R_7 represents an alkoxy group,
- R_8 and R_9 together constitute an extra bond,
  or R_8 and R_{13} together constitute a sulphide bridge, in which case R_9 and R_{10} together constitute an oxo group and R_{14} represents a chlorine atom,
- R_{10} represents an alkoxy group,
- R_{11} represents a hydroxy or alkoxy group,

- R_{12} represents a hydrogen atom,
  or R_{11} and R_{12} together constitute an oxo, oxime or O-alkyl-oxime group,
- R_{13} and R_{14} each represent a hydrogen atom or together constitute an oxo group,

with the proviso that the compound of formula (I) cannot represent :

- spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumine)
- spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-acetylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-hydroxy-cyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol]
- spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-benzoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(4S,5S)-4-acetyl-cyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumidine)
- spiro[4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]
- spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

and wherein it should be understood that

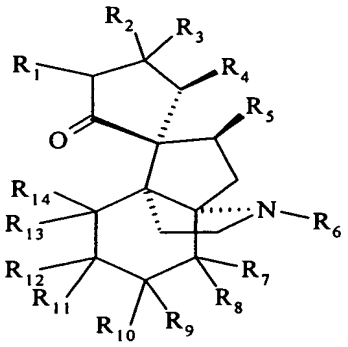
- "alkyl" denotes an alkyl group containing 1 to 6 carbon atoms, which may be linear or branched,
- "alkoxy" denotes an alkoxy group containing 1 to 6 carbon atoms, which may be linear or branched,
- "aryloxy" denotes an aryloxy group wherein the aryl moiety represents phenyl or naphthyl,
- "aroyl" denotes an arylcarbonyl group wherein the aryl moiety represents phenyl or naphthyl,

and further relates to the enantiomers and diastereoisomers thereof, and to their addition salts with pharmaceutically acceptable acids or bases.

Without imposing any restriction, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, methanesulphonic acid, camphoric acid and oxalic acid. may be mentioned as pharmaceutically acceptable acids.

Without imposing any restriction, sodium hydroxide, potassium hydroxide, triethylamine and tert-butylamine may be mentioned as pharmaceutically acceptable bases.

The preferred configuration of the compounds of formula (I) claimed for the invention is shown by formula (I') :



(I').

The preferred compounds of the invention are compounds of formula (I) wherein on the one hand R_1 and R_2, and on the other hand R_8 and R_9, together constitute an extra bond.

The preferred meaning of the groups R_3, R_7 and R_{10} in the compounds of formula (I) of the invention is the methoxy group.

R_4 advantageously represents a hydroxy, acetyloxy or benzoyloxy group.

Very preferably, R_5 represents a chlorine atom.

R_6 more specifically represents a methyl or ethyl group or a hydrogen atom.

The invention preferably relates to compounds of formula (I) wherein R_{11} and R_{12} together constitute an oxo group.

More especially, R_{13} and R_{14} each represent a hydrogen atom.

The invention more advantageously relates to the following compounds of formula (I) :

spiro[(4S,5S)-4-(ethoxycarbonyl)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-ethylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-(ethoxycarbonyl)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-propanoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one oxime],

spiro[(4S,5S)-3,4-dimethoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-2,3,3a,7a-tetrahydro-4*H*,5*H*-indene-4,5-dione],

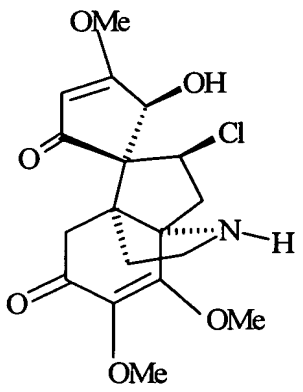
spiro[(5S)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-hydroxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol],

spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2,4-dichloro-3aS, 7aS-((2,3)-1-methylpyrrolidine)-7-methoxy-8-thiabicyclo[2.2.1]-1,2,3,3a,4,7a-hexahydro-5*H*,6*H*-indene-5,6-dione].

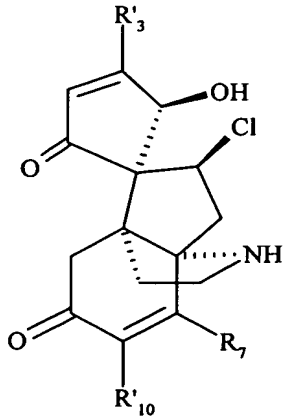
The enantiomers and diastereoisomers of the preferred compounds of the invention and their addition salts with pharmaceutically acceptable acids or bases constitute the entire invention.

The invention further relates to a method of preparing the compounds of formula (I), the said method being characterised in that the compound of formula (II) (acutumidine) is used as starting material:



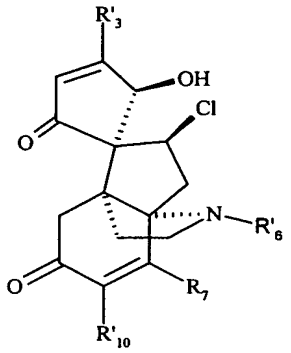
(II),

the compound of formula (II) is successively subjected to the action of a demethylating agent and an alkylating agent to obtain the compound of formula (I/a), a particular case of the compounds of formula (I) :



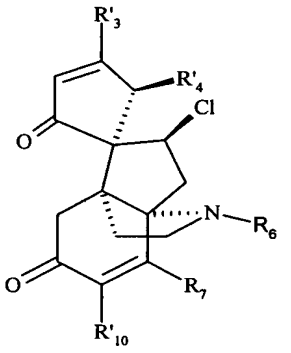
(I/a),

wherein R'_3 and R'_{10} each represent an alkoxy group and R_7 is as defined for formula (I),
which compound (I/a) may be reacted with a compound of formula $R_{15}CHO$ (wherein R_{15} represents an alkyl group) in a reducing medium to obtain the compound of formula (I/b), a particular case of the compounds of formula (I) :



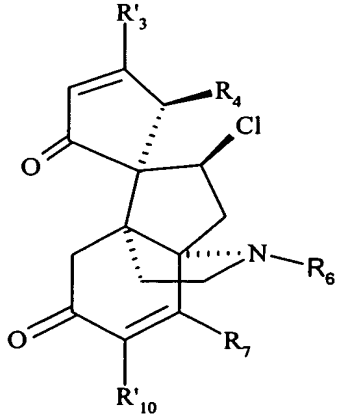
(I/b),

wherein R'_3, R_7 and R'_{10} are as hereinbefore defined and R'_6 represents an alkyl group; the compounds of formula (II), (I/a) or (I/b) may be reacted with a compound of formula $(R_{16}CO)_2O$ (wherein R_{16} represents an alkyl or aryl group) to obtain the compound of formula (I/c), a particular case of the compounds of formula (I) :



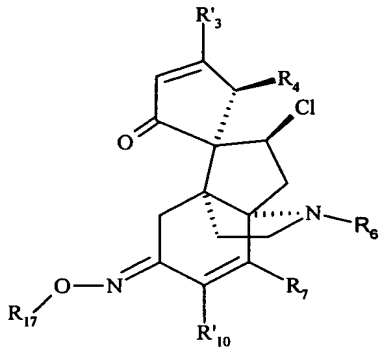
(I/c),

wherein R'_3, R_7 and R'_{10} are as hereinbefore defined, R_6 is as defined for formula (I) and R'_4 represents a hydroxy, alkylcarbonyloxy or arylcarbonyloxy group;
or the compounds of formula (II), (I/a), (I/b) or (I/c) may be reacted with a compound of formula E-R_{15} (wherein R_{15} represents an alkyl group and E represents a leaving group such as a halogen atom or a tosyl group) to obtain the compound of formula (I/d), a particular case of the compounds of formula (I) :



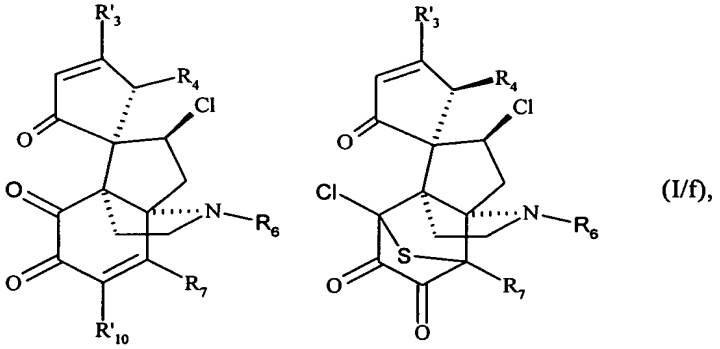
(I/d),

wherein R'_3, R_6, R_7 and R'_{10} are as defined hereinbefore and R_4 is as defined for formula (I);
the compound of formula (I/d) may be reacted with the compound of formula $R_{17}ONH_2$ (wherein R_{17} represents a hydrogen atom or an alkyl group) to obtain the compound of formula (I/e), a particular case of the compounds of formula (I) :



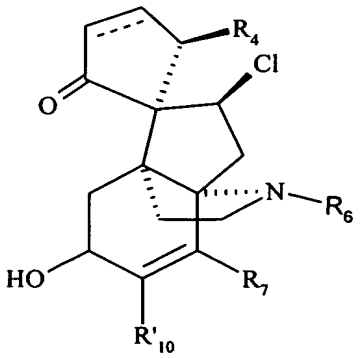
(I/e),

wherein R'_3, R_4, R_6, R_7, R'_{10} and R_{17} are as hereinbefore defined;
or the compound of formula (I/d) may be reacted with $SOCl_2$/DMF to obtain the compounds of formula (I/f), particular cases of the compounds of formula (I) :



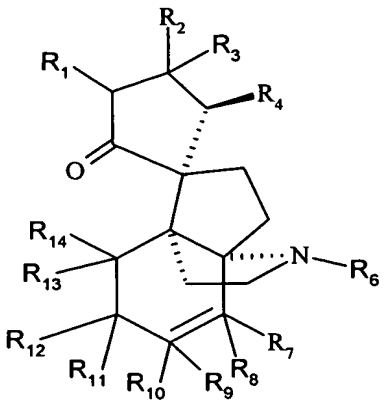
(I/f),

wherein R'_3, R_4, R_6, R_7 and R'_{10} are as hereinbefore defined;
or the compound of formula (I/d) may be reacted with a reducing agent such as $LiAlH_4$ to obtain the compound of formula (I/g), a particular case of the compounds of formula (I) :



(I/g),

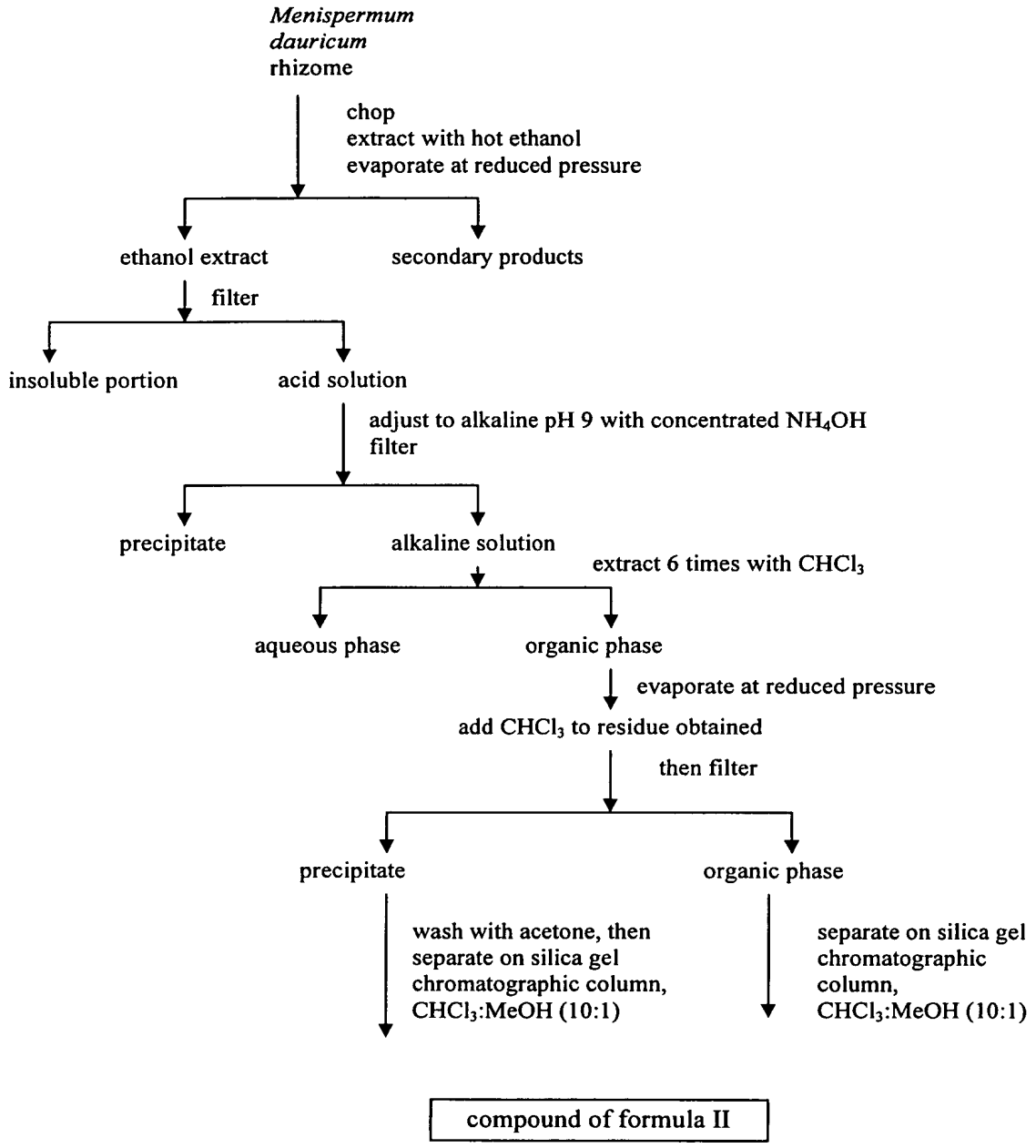
wherein R_4, R_6, R_7 and R'_{10} are as hereinbefore defined and the symbol ----- indicates that the bond in question may be a single or a double bond;
or the compound of formula (I/d), (I/e), (I/f) or (I/g) may be reacted with n-Bu_3SnH in the presence of AIBN to obtain the compounds of formula (I/h), particular cases of the compounds of formula (I):



(I/h),

wherein R_4, R_6 and R_7 are as hereinbefore defined and R_1, R_2, R_3, R_5, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are as defined for formula (I), and
the compounds of formulae (Ia) to (Ih) constitute the totality of the compounds of the invention, which may be purified in accordance with conventional separation techniques and if necessary, converted into their addition salts with pharmaceutically acceptable acids or bases and where appropriate separated into their isomers in accordance with conventional separation techniques.

Persons skilled in the art may obtain the compound of formula (II) by extracting rhizomes of *Menispermum dauricum* in accordance with the sequence of scheme 1:



Scheme 1: Extraction of compound of formula II

Apart from their novelty, the compounds of the invention have the property of stimulating the cognitive process, enabling them to be used for the treatment of cognitive deficit associated with cerebral ageing and neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

The invention also relates to pharmaceutical compositions comprising at least one of the compounds of formula (I) as the active component together with one or more suitable inert, non-toxic excipients.

Furthermore, the Applicant has found that acutumine and/or acutumine compounds have mnemocognitive enhancement properties.

The invention accordingly relates also to the use of acutumine and/or acutumine compounds in the preparation of pharmaceutical compositions for use in the treatment of cognitive deficit associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

More particularly, the invention relates to the use of acutumine and/or acutumine compounds in the preparation of pharmaceutical compositions, the said pharmaceutical compositions being used for the treatment of cognitive deficit associated with cerebral ageing and neurodegenerative diseases, wherein the compounds are, for example:

spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumine),

spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-acetylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-hydroxycyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol],

spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-benzoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-acetylcyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumidine),

spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one],

spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one].

An advantageous aspect of the invention relates to the use of acutumine in preparing pharmaceutical compositions for use in the treatment of cognitive deficit associated with cerebral ageing and neurodegenerative diseases.

Another especially advantageous aspect of the invention relates to the use of the following compounds in preparing pharmaceutical compositions, the said compositions being used for the treatment of cognitive deficit associated with cerebral ageing and neurodegenerative diseases:

spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-acetyl-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-acetylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-hydroxycyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol], spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-(benzoyloxy)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-benzoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-

hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-acetylcyclopentan-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one] (acutumidine), spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one], and spiro[(5S)-2-methoxy-2-cyclopenten-1-one-5:3-2-chloro-3aS,7aS-((2,3)-1*H*-pyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one].

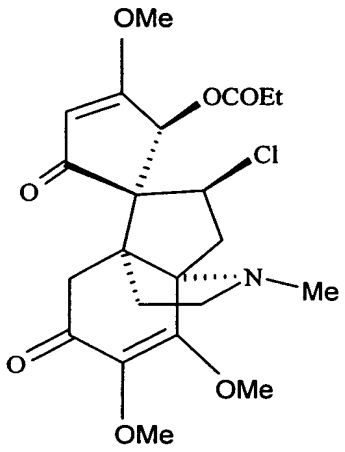
The invention relates also to pharmaceutical compositions comprising acutumine or its compounds and one or more pharmaceutically acceptable excipients, the said compositions being used for the treatment of cognitive deficit associated with cerebral ageing and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Pick's disease, Korsakoff's psychosis, and frontal lobe and subcortical dementias.

Of the pharmaceutical compositions claimed for the invention, particular mention may be made of those suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, in the form of tablets or sugar-coated pills, sublingual tablets, gelatin capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions, etc..

The useful dosage can be varied according to the nature and severity of the disorder, the route of administration and the age and weight of the patient. The daily dosage varies from 0.01 mg to 1 g, given in a single or divided dose.

The following Examples illustrate but in no way limit the invention.

Example 1 : Spiro[(4S,5S)-4-(ethoxycarbonyl)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]



Step A : Spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]

The compound of formula (II) 1 g is dissolved in HCOOH (10 ml) and stirred with formaldehyde 10 ml at 40-50°C for 4 hours. The reaction mixture is then rendered alkaline with NH_4OH until the pH is 8-9. The white precipitate formed is filtered off and then dried with K_2CO_3 to obtain the title compound.

Step B : Spiro[(4S,5S)-4-(ethoxycarbonyl)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]

One gramme of the compound obtained in Step A is dissolved in $CHCl_3$ and DMF. Propanoic anhydride 2 ml is then added dropwise and the reaction mixture is stirred overnight. Saturated $NaHCO_3$ solution is then added until the pH is 8-9 and the reaction mixture is extracted with $CHCl_3$. The residue obtained after evaporating off the solvent is purified by silica gel chromatography ($CHCl_3$:Me_2CO / 20:11) to obtain the title compound.

Melting point : 156-158°C

Elemental microanalysis :

	C	H	N
% calculated :	58.21	6.22	3.09
% found :	58.00	6.27	3.03

Example 2: Spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-ethylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]

The compound of formula (II) 50 mg is dissolved in HCOOH (0.5 ml) and stirred with acetaldehyde 0.5 ml at 40-50°C for 6 hours. The reaction mixture is then rendered alkaline with NH_4OH until the pH is 8-9 and extracted with $CHCl_3$. The residue obtained after evaporating off the solvent is purified by silica gel chromatography ($CHCl_3$:Me_2CO/2:1) to obtain the title compound.

Melting point : 156-158°C

Elemental microanalysis :

	C	H	N
% calculated :	58.32	6.31	3.40
% found :	57.98	6.31	3.09

Example 3 : Spiro[(4S,5S)-4-(ethoxycarbonyl)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-propanoylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]

The compound of formula (II), 1 g, is dissolved in *N,N*-dimethylaminopyridine and 2 ml of $CHCl_3$. Acetic anhydride 2 ml is then added dropwise and the reaction mixture is stirred overnight at ambient temperature. Saturated $NaHCO_3$ solution is then added until the pH is 8-9 and the reaction mixture is extracted with $CHCl_3$. The residue obtained after evaporating off the solvent is purified by silica gel chromatography ($CHCl_3$:Me_2CO / 20:11) to obtain the title compound.

Melting point : 166-168°C

Elemental microanalysis :

	C	H	N
% calculated :	58.12	6.09	2.82
% found :	57.55	6.03	2.72

Example 4 : Spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one oxime]

One gramme of the compound obtained in Step A of Example 1 is stirred with hydroxylamine 1 g in ethanol 15 ml at 70-80°C for 4 hours. Saturated $NaHCO_3$ solution is then added until the pH is 8-9 and the reaction mixture is extracted with $CHCl_3$. The residue obtained after evaporating off the solvent is purified by silica gel chromatography ($CHCl_3$:Me_2CO / 3:1) to obtain the title compound in the form of a white solid.

Melting point : 211-213°C

Elemental microanalysis :

	C	H	N
% calculated :	55.27	6.10	6.79
% found :	55.17	5.79	7.46

Example 5 : Spiro[(4S,5S)-3,4-dimethoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]

The compound obtained in Step A of Example 1 (200 mg) is dissolved in DMSO and stirred with NaOH 100 mg and CH_3I 1 ml at ambient temperature for 20 minutes. The reaction mixture is then diluted with water 5 ml and then with $CHCl_3$. The residue obtained after extraction and evaporating off the solvent is purified by silica gel chromatography ($CHCl_3$:MeOH / 20:1) to obtain white needles of the title compound.

Melting point : 165-167°C

Elemental microanalysis :

	C	H	N
% calculated :	57.32	6.36	3.40
% found :	57.18	6.38	3.86

Example 6 : Spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-2,3,3a,7a-tetrahydro-4*H*,5*H*-indene-4,5-dione]

The compound obtained in Step A of Example 1 (30 mg) is dissolved in $SOCl_2$ and stirred with DMF (catalyst) at 85°C for 30 minutes. The crude reaction mixture is purified by silica gel chromatography ($CHCl_3$:Et_2O/10:1) to obtain the title compound.

Melting point : 152-154°C

Example 7 : Spiro[(5S)-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one]

The title compound was isolated by silica gel chromatography starting with the ethanolic extract obtained from *Menispermum dauricum* rhizome.

Melting point : 174-176°C

Example 8 : Spiro[(4S,5S)-4-hydroxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-ol]

The compound obtained in Step A of Example 1 (50 mg) is dissolved in THF (15 ml) and stirred with $LiAlH_4$ at ambient temperature for 2 hours. The crude reaction mixture is diluted with water, extracted with $CHCl_3$ and then purified by silica gel chromatography to obtain the title compound.

Example 9 : Spiro[(4R,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2,4-dichloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-7-methoxy-8-thiabicyclo[2.2.1]-1,2,3,3a,4,7a-hexahydro-5*H*,6*H*-indene-5,6-dione]

The procedure is the same as in Example 6 (two compounds (Examples 6 and 9) are formed in the same reaction sequence).

Melting point : 214-216°C

Pharmacological Study of the Compounds of the Invention

Example A: Acute toxicity study

The acute toxicity after oral dosing of mice (26 ± 2 g) in groups of eight was evaluated. The animals were observed at regular intervals in the course of the first day following treatment and once daily for 2 weeks thereafter. The LD_{50} (the dose resulting in 50 % mortality) was evaluated and demonstrated that the compounds of the invention had low toxicity.

Example B: Morris water maze test in mice

The anti-amnesic effect of the compounds of the invention was evaluated using the Morris water maze test (Morris *et al.*, Nature, 1986, 319, 774-776) with scopolamine as amnestic agent. Kunming mice (18-24 g, Shanghai Experimental Animal Centre) of either sex were used. Mice were placed on the water maze (80x50x20 cm) and trained to find the platform. After one day's acclimation, each mouse received three training runs per day for seven days. Mice were trained to a standard at which they found the platform within 20 seconds with <2 errors of entering a dead-end. Once a mouse met the standard, training was reduced to once daily until all the mice met the standard. Trained mice were randomly divided into groups. The compounds under study were dissolved in distilled water and given by the oral route 40 minutes before behavioural testing. Scopolamine (5 mg/kg, i.p.) was injected 30 minutes before the test. The number of errors and the time taken to reach the platform were recorded. Data were expressed as mean +/- s.e.m. ANOVA was used for statistical analysis, after which Duncan's multiple-range test was applied.

The results demonstrated that the compounds of the invention were able to counteract scopolamine-induced decline in memory in dose-dependent fashion (20-100 mg/kg) in the Morris water maze test on mice, indicating that compounds of this kind have anti-amnesic properties.

Example C : Social recognition in the Wistar rat

The social recognition test was first described by Thor and Holloway in 1982 (J. Comp. Physiol., 1982, 96, 1000-1006), since when its use in studying the mnemocognitive effects of new compounds has been proposed by various authors (Dantzer *et al.*, Psychopharmacology, 1987, 91, 363-368 ; Perio *et al.*, Psychopharmacology, 1989, 97, 262-268). The test is based on the natural expression of olfactory memory in the rat and its natural tendency to forget, memorisation being evaluated by the recognition of a congeneric juvenile by an adult rat. A randomly chosen juvenile rat (21 days) is left for 5 minutes in a cage housing an adult rat. The investigator observes the social recognition behaviour of the adult rat with the aid of video equipment and measures the overall duration. The juvenile rat is then removed from the adult rat's cage and placed in its own cage until the second introduction. The adult rat is given the compound under test and after 2 hours is brought into contact with the juvenile rat again (5 minutes). The social recognition behaviour is re-observed and its duration measured. The assessment criterion is the difference (T_2-T_1) in seconds between the "recognition" times in the 2 encounters.

The results obtained showed that difference (T_2-T_1) ranged from (–20) s to (–45) s for doses of 3 to 30 mg/kg, indicating that the compounds of the invention greatly enhance memorisation.

Example D : Object recognition in the Wistar rat

The object recognition test in the Wistar rat was initially developed by Ennaceur and Delacour (Behav. Brain Res., 1988, 31, 47-59). The test is based on the animal's spontaneous exploratory activity, which has the characteristics of episodic memory in humans. This memory test is sensitive to ageing (Scali *et al.*, Eur. J. Pharmacol., 1997, 325, 173-180) and cholinergic dysfunction (Bartolini *et al.*, Pharm. Biochem. Behav. 1996, 53(2), 277-283) and is based on differences in the exploration of two objects of reasonably similar shape – one familiar, the other new. Prior to the test, the animals are allowed to adapt to the environment (an enclosure without an object). In the first stage, the rat is left (for 3 minutes) in the enclosure, in which there are two identical objects. The duration of exploration is recorded for each object. Twenty-four hours later, in the second stage (3 minutes), one of the two objects is replaced with a new object. The duration of exploration is recorded for each object. The assessment criterion is the difference δ in seconds between the exploration times for the new object and the familiar object in the second stage. Control animals pre-treated with the vehicle via the i.p. route 30 minutes before each stage explore the familiar object and the new object in an identical manner, signifying that the object introduced earlier has been forgotten. Animals treated with a compound stimulating mnemocognition preferentially explore the new object, signifying that the object introduced earlier has been remembered.

The results obtained show that the difference δ was 5 to 10 s for doses from 3 to 30 mg/kg, indicating that the compounds of the invention greatly enhance memorisation.

Example E : Pharmaceutical composition

Recipe for the preparation of 1000 tablets (each containing 10 mg of active component):

spiro[(4S,5S)-4-hydroxy-3-methoxy-2-cyclopenten-1-one-5:3(2S)-2-chloro-3aS,7aS-((2,3)-1-methylpyrrolidine)-6,7-dimethoxy-1,2,3,3a,4,7a-hexahydro-5*H*-inden-5-one oxime] (Example 4) ..... 10 g
hydroxypropylcellulose ..... 2 g
wheat starch ..... 10 g
lactose ..... 100 g
magnesium stearate ..... 3 g
talc ..... 3 g